

**Opinion of the Scientific Panel on Food Additives,
Flavourings, Processing Aids and Materials in Contact with Food (AFC)
on a request from the Commission related to**

Ethyl Cellulose as a food additive

Question number EFSA-Q-2003-116

adopted on 17 February 2004

SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food has been asked to evaluate the safety of ethyl cellulose.

Ethyl cellulose is a widely used excipient in pharmaceutical applications. Its use is presently requested in the formulation of food supplements in dry applications e.g. as a controlled release agent and protective colloid and as a thickener/binder in hydrophobic matrices. The substance is also intended to be used as an emulsion stabiliser in water/oil systems and as a barrier layer to control the diffusion of ingredients in e.g. pizza preparations.

The Scientific Committee on Food (SCF) has already evaluated a number of modified celluloses before. In 1994 an Acceptable Daily Intake of "not specified" was allocated by the SCF to five closely related cellulose derivatives i.e. methyl cellulose (E461), hydroxypropyl cellulose (E463), hydroxypropyl methyl cellulose (E464), ethyl methyl cellulose (E465) and carboxymethyl cellulose (E466).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has also evaluated modified celluloses. In 1990 JECFA allocated a group ADI "not specified" to seven modified cellulose derivatives including ethyl cellulose.

In its evaluation the Panel noted that toxicological data on modified celluloses, e.g. data on acute toxicity, subchronic and chronic toxicity and genotoxicity as well as reproductive and developmental toxicity can be found in a number of reviews.

An additional oral subchronic study on an aqueous dispersion of ethyl cellulose in the rat was submitted.

The Panel evaluated ethyl cellulose on the basis of the safety data of the whole group of closely related cellulose derivatives. The Panel considers that during the manufacturing process, the steaming and drying steps would remove volatile residues including ethyl chloride. Taking into account the strong hydrophobic character of ethyl cellulose together with its high molecular mass (above 500 kD) the Panel also considers that ethyl cellulose will pass essentially unchanged through the gastrointestinal tract following oral ingestion and that adverse effects are unlikely. The Panel decided to include ethyl cellulose in the group ADI "not specified" for modified celluloses established by the SCF.

KEY WORDS

Ethyl Cellulose, Modified cellulose, Food additive, INS 462, CAS Registry Number 9004-57-3

BACKGROUND

The European Commission has received a request to evaluate the safety of ethyl cellulose. According to the petitioner ethyl cellulose is a widely used excipient in pharmaceutical applications and has monographs in the European and in the United States Pharmacopoeia. Ethyl cellulose is considered having unique properties in the formulation of food supplements in dry applications, which are defined as food categories in the European Union, i.e. as a coating agent for solid dietary food supplements and as a micro-encapsulating agent for fixing colours and flavouring agents. In order to be able to use it for the fore-mentioned applications it would have to be included in the European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners.

The EU Scientific Committee on Food (SCF) evaluated five closely related cellulose derivatives i.e. methyl cellulose (E 461), hydroxypropyl cellulose (E463), hydroxypropyl methyl cellulose (E464), ethyl methyl cellulose (E465) and carboxy methyl cellulose (E466). An Acceptable Daily Intake of "not specified" was allocated and these food additives have been included in Annex I of the EU directive 95/2/EC (SCF 1994).

In its evaluation the SCF considered the total set of data covering seven modified celluloses (the five listed above, ethyl cellulose and ethylhydroxyethyl cellulose (EHEC)) but did not include ethyl cellulose and EHEC in the final evaluation, as an opinion on these specific celluloses was not required at that time.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) also evaluated initially the five modified celluloses and established a group ADI of 0-25 mg/kg bw (JECFA 1974). At later meetings, JECFA decided that this group ADI should also apply to ethyl- and ethylhydroxyethyl cellulose (JECFA 1982; JECFA, 1983). At the 35th meeting, a group ADI "not specified" was allocated to these seven modified cellulose derivatives (JECFA 1990).

TERMS OF REFERENCE

The Commission asks the EFSA to issue an opinion on the safety in use of ethyl cellulose as a food additive

ASSESSMENT

CHEMISTRY

Ethyl cellulose is the ethyl ether of cellulose. Cellulose is a high molecular weight linear homopolymer of about 3000 β -D-glucopyranosyl repeating units joined by (1→4) glycosidic linkages. Its molecular mass is above 500.000 Dalton. It is insoluble in water.

Ethyl cellulose is a free flowing white to light tan powder. The percentage of ethoxy groups (-OC₂H₅) in the molecule varies between 44% and 51% on a dry weight basis (equivalent to not more than 2.6 ethoxyl groups on average per anhydroglucose unit). Its CAS Registry number is 9004-57-3.

Manufacturing process

According to the petitioner, ethyl cellulose is prepared from wood pulp or cotton by treatment with alkali and ethylation of the alkali treated cellulose with ethyl chloride. The resulting product is then further steamed and dried.

PURITY

According to the petitioner the loss on drying (105°C, 2 hours) is not more than 3%, the sulphated ash content not more than 0.4%, arsenic content not more than 3 mg/kg, lead content not more than 10mg/kg, other heavy metals not more than 40mg/kg.

According to the petitioner ethyl cellulose complies with the purity requirements of the US Food Chemical Codex. (FCC 2003)

CASE OF NEED AND PROPOSED USES

Ethyl cellulose is already widely used as a pharmaceutical excipient in solid dosage forms where it has the functionality of a binder and/or filler substance in tablets.

The petitioner intends to use ethyl cellulose in a number of specific applications:

- as a thickener or binder in hydrophobic matrices (e.g. solid dietary supplements),
- as an emulsion stabiliser in (salad) dressings,
- as a barrier layer controlling diffusion of ingredients in e.g. pizza preparations,
- as a taste masking agent in some dietary food supplements.
- as a micro-encapsulation agent specifically used in cases when water-soluble products cannot be used because of processing problems or water sensitivity of the active ingredient,

EXPOSURE

The petitioner has submitted following exposure estimates:

- The use of ethyl cellulose as thickener/binder is restricted to foodstuffs in tablet form at a typical level of 300 mg per tablet of 1000 mg. The maximum intake assumption by the petitioner is 3 tablets per day leading to an intake of 900 mg ethyl cellulose. Assuming a body weight of 60 kg this would result in a human intake of 15 mg/kg bw/day.
- A film coating for a vitamin preparation contributes to around 10 % of the weight. The ethyl cellulose content in the film is approximately 30 %. For a 1000 mg tablet, this results in 30 mg ethyl cellulose per tablet. According to the petitioner a typical intake for this application is 5 tablets per day, which would result in a daily exposure of 150 mg ethyl cellulose or an intake of 2.5 mg/kg bw/day.
- The use level of ethyl cellulose as emulsion stabiliser in a salad dressing is 0.2%. Assuming a serving of 100 g per day this would lead to a daily intake of 200 mg ethyl cellulose/day or 3.3 mg/kg bw/day.
- The migration control layer in a pizza is about 50 gram. The use level of ethyl cellulose in the layer is 0.3%. Assuming an intake of one pizza/day the intake of ethyl cellulose would be 150 mg or 2.5 mg/kg bw/day.

The total estimated intake of ethyl cellulose from these applications would according to the petitioner amount to around 25 mg/kg bw/day. This estimate does not take into account the use of ethyl cellulose as a micro-encapsulation agent (no data were provided). The petitioner argues that this estimate is an over-estimate of the potential total exposure to ethyl cellulose since it

was assumed that all products (foodstuffs, food supplement tablets) contained ethyl cellulose at the maximum specified level of use. The Panel agrees with the petitioner that this intake is likely to be an over-estimate of the human intake.

INFORMATION ON EXISTING AUTHORIZATIONS AND EVALUATIONS

The situation on the existing authorisations has already been explained in the background section.

In the Codex Alimentarius system ethyl cellulose is listed as number 462 in the International Numbering System (INS).

BIOLOGICAL AND TOXICOLOGICAL DATA

Except for a new study, original papers were not provided. However, toxicological data on modified celluloses, e.g. data on acute toxicity, subchronic and chronic toxicity and genotoxicity as well as reproductive and developmental toxicity can be found in a number of reviews (e.g. JECFA 1974; JECFA 1990; SCF 1992; SCF 1999).

Absorption

According to the petitioner no specific studies are known. However, there is a close structural relationship with the other evaluated cellulose derivatives {i.e. methyl cellulose (E 461), hydroxypropyl cellulose (E463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465) and carboxy methyl cellulose (E 466)}. Taking into account the hydrophobic character of ethyl cellulose and also taking into account the high molecular mass of ethyl cellulose, the Panel considers that this cellulose derivative will pass essentially unchanged through the gastrointestinal tract following oral ingestion.

Toxicity data

The reviews include limited data on ethyl cellulose, e.g. a study, in which no adverse effects (as judged by appearance, behaviour, growth and gross and microscopic examination of the tissues) were reported in a group of 80 rats that were maintained for 8 months on a diet containing 1.2% ethyl cellulose, which amounted to an average dose of 182 mg/rat/day equivalent to approximately 600 mg/kg bw/day. (Hake and Rowe 1963).

With the petition, an additional subchronic study with an aqueous dispersion of ethyl cellulose was provided. In this study, an undiluted dispersion of ethyl cellulose (Aquacoat®ECD) containing cetyl alcohol and sodium lauryl sulphate as stabilisers was administered to groups of 20 male and 20 female Sprague-Dawley rats by oral gavage at doses of 903, 2709 or 4515 mg/kg bw/day (dry weight basis) for 90 days. Control animals received water at the same dosage volume as the high-dose group. Body weights and food consumption were recorded weekly. Blood was collected prior to study termination for haematology and clinical chemistry measurements. Survivors underwent complete necropsies on days 91-94. Selected organs were weighed and histologically examined. The only treatment-related clinical sign observed was pale faeces, which was noted among males and females receiving 2709 and 4515 mg/kg bw/day Aquacoat®ECD. No statistically significant differences in body weights, body weight gains, food consumption and organ weights were noted among males and females when compared with controls. No treatment-related effects in haematology parameters were noted. Significantly decreased total protein and globulin levels and increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were seen in male rats receiving 2709 and 4515 mg Aquacoat®ECD/kg bw/day. No gross or microscopic lesions were attributed to Aquacoat®ECD treatment. Under the conditions of this study the no-observed-adverse-effect level (NOAEL) of

the total solids in the Aquacoat®ECD dispersion for female rats was in excess of 4515 mg/kg bw/day: the NOAEL for male rats is 903 mg/kg bw/day (Kotkoskie and Freeman 1998). The authors suggest that the observed effects on liver enzymes are likely attributable to the cetyl alcohol component. Cetyl alcohol has been shown to raise the serum AST levels in dogs. It should be noted that cetyl alcohol is not a permitted food additive and that the substance is not present in the additive under consideration.

CONCLUSION AND RECOMMENDATION

The Panel evaluated ethyl cellulose on the basis of the safety data of the whole group of closely related cellulose derivatives. The Panel considers that during the manufacturing process, the steaming and drying steps would remove volatile residues including ethyl chloride. Taking into account the strong hydrophobic character of ethyl cellulose together with its high molecular mass (above 500 kD) the Panel also considers that ethyl cellulose will pass essentially unchanged through the gastrointestinal tract following oral ingestion and that adverse effects are unlikely. The Panel decided to include ethyl cellulose in the group ADI “not specified” for modified celluloses established by the SCF (SCF 1992; SCF 1999).

DOCUMENTS PROVIDED TO EFSA

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